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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 1.2004.0347/ZAR	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/ES2004/000320	International filing date *(day/month/year)* 05.07.2004	Priority date *(day/month/year)* 22.08.2003
International Patent Classification (IPC) or national classification and IPC C07K7/06		
Applicant PROYECTO DE BIOMEDICA CIMA S.L. et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 9 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 3 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
21.03.2005	15.09.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Vanmontfort, D Telephone No. +49 89 2399-8457

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/ES2004/000320

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☒ This report is based on translations from the original language into the following language english, which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☒ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-27 as originally filed

   Claims, Numbers

   1-17 as amended (together with any statement) under Art. 19 PCT

   Drawings, Sheets

   1/5-5/5 as originally filed

   ☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 16

because:

☒ the said international application, or the said claims Nos. 16 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation to restrict or pay additional fees, the applicant has:
   - ☐ restricted the claims.
   - ☐ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-17
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-17
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-15,17
	No:	Claims	

2. Citations and explanations (Rule 70.7):

   see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed

   ☐ filed together with the international application in computer readable form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment on

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

Section III

Claim 16 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Section IV

This Authority considers that there are 20 inventions covered by the claims indicated as follows:

1. Claims 1-17 (partially)

   a peptide characterized by its TGF-beta1 binding capacity and having an amino acid SEQ ID 1, a pharmaceutical composition comprising said peptide, its corresponding DNA sequence and the use of said peptide to treat fibrosis.

2. Claims 1-17 (partially)

   a peptide characterized by its TGF-beta1 binding capacity and having an amino acid SEQ ID 17 or SEQ ID 24-36, a pharmaceutical composition comprising said peptide, its corresponding DNA sequence and the use of said peptide to treat fibrosis.

3-20. Claims 1-17 (partially)

   a peptide characterized by its TGF-beta1 binding capacity and having respectively amino acid sequences SEQ ID 2-6, 9-16 or 18-22, a pharmaceutical composition comprising said peptide, its corresponding DNA sequence and the use of said peptide to treat fibrosis.

The single general inventive concept linking together the 20 inventions is a TGF-

beta1 binding protein. Said proteins are known from D4 (see below for reference; claims).
Consequently, the common linking concept is anticipated by this document and therefore not novel.
Hence, the examining division considers that the separate inventions are not so linked as to form a single general inventive concept according to Rule 13.1 PCT. No furhter technical feature could be identified which could be considered as a special technical feature in the sense of Rule 13.2 PCT.

Section V

2.1 Reference is made to the following documents:

D1: JP-A-8 151 396 11 June 1996
D2: WO 00 24782 A2
D3: ISHIKAWA, D. ET AL.: 'Gdlalpha-replica peptides functionally mimic Gdlalpha, an adhesion molecule of metastatatic tumor cells, and suppress the tumor metastasis' FEBS LETTERS vol. 441, 1998, pages 20 - 24
D4: ES-A1-2 146 552

2. The application does not meet the requirements of Article 6 PCT for the following reasons:

2.1 The term "fragment of said peptides comprising 3 to 15 amino acids" is vague and unclear and leave the reader in doubt as to the meaning of the technical features to which they refer, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT). The particular identifying characteristics of said fragment (sequence ID's) should be included in order to exclude variants which do not have the TGFbeta1 binding capacity.

2.2 Second medical use claims 4, 5 and 17 is not acceptable under Art. 6 PCT. The therapeutic application is functionally defined by a mechanism of action which does not allow any practical application in the form of a defined, real treatment of a pathological condition (disease).

The objection could be overcome by either introducing in the claims a list of pathological conditions (diseases) cited in the application, or by showing that means are available which would allow the skilled person to recognise which additional condition(s) would fall within the functional definition (C-III, 6.5).

3. If the above-mentioned objections were overcome, the following should be noted with respect to novelty (Article 33(2) PCT) and inventive step (Article 33(3) PCT).

3.1 D1 discloses sequence 7 of the invention (sequence 66 of D1). There is no disclosure about the capacity of said sequence to bind TGF-beta1.

D2 discloses sequence 8 of the invention (sequence 1099 of D2). There is no disclosure about the capacity of said sequence to bind TGF-beta1.

D3 discloses sequence 8 of the invention (sequence 3 of Table 1). There is no disclosure about the capacity of said sequence to bind TGF-beta1.

D4 (claims) discloses inhibitors of TGF-beta1 and the use of said inhibitors to treat fibrosis.

3.2 The subject-matter of claims 1-3 and 8-17 is novel and inventive (Articles 33(2) & 33(3) PCT).
None of the available prior art documents discloses or refers to any of the sequences as claimed in claims 1-3. The same applies to claims 8-17, which are dependent on claims 1-3.

3.3 The subject-matter of claims 4-7 is novel and inventive (Articles 33(2) & 33(3) PCT). D4, which is considered to represent the closest prior art, discloses inhibitors of TGF-beta1 and the use of said inhibitors to treat fibrosis (claims). The subject-matter of claim 4 differs in the claimed TGF-beta1 inhibitors. The problem to be solved can therefore be formulated as the provision of an alternative method to provide a medicament to treat fibrosis. There is no indication in any of the available prior art that the claimed sequences can be used to treat fibrosis. Although sequence 7 and 8 are known from D1-D3, there is no guidance for the person skilled in the art that said

sequences have TGF-beta1 activity and that they can be used to treat fibrosis. Therefore, it would not be obvious for one skilled in the art to introduce this feature in the closest prior art to solve the problem posed. Hence, the subject-matter of claim 4 is considered to involve an inventive step (Article 56 EPC). The same applies to dependent claims 5-7.

4. For the assessment of the present claim 16 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

MODIFIED ACCORDING TO ARTICLE 19(1): CLAIMS

1. A peptide characterized by it's capacity to bind whose amino acid sequence is selected from any one c ID NO:1-SEQ ID NO:6, SEQ ID NO:9-SEQ ID NO: 22, and ID NO:24-SEQ ID NO:36, or fragments of said peptic comprising 3 to 15 amino acids, and thei. pharmaceutically acceptable salts.

2. Peptide according to claim 1, characterized in that it also has the capacity to inhibit the biological activity of TGF-β1 *in vitro* and/or *in vivo*.

3. Peptide according to either claim 1 or 2, selected from the group formed by peptides indentified as SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 11, SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 33, SEQ ID NO: 34, and their pharmaceutically acceptable salts.

4. Use of a peptide whose amino acid sequence is selected from any one of sequences SEQ ID NO: 1 to SEQ ID NO: 22, and, SEQ ID NO: 24 to SEQ ID NO: 36, or fragments of said peptides comprising 3 to 15 amino acids, and their pharmaceutically acceptable salts, in the manufacture of a pharmaceutical composition with the capacity to inhibit TGF-β1's biological activity.

5. Use of a peptide according to claim 4, in the manufacture of a medicament for the treatment of diseases or pathological alterations associated with excessive or deregulated expression of TGF-β1.

6. Use of a peptide according to claim 5, characterized in that said diseases or pathological alterations associated with excessive or deregulated expression of TGF-β1, comprise fibrosis associated with loss of function in an

organ or tissue, and surgical and/or esthetic complications.

7. Use of a peptide according to any of claims 5 or 6, characterized in that said diseases or pathological alterations associated with excessive or deregulated expression of TGF-β1, are selected from among pulmonary fibrosis, hepatic fibrosis (cirrhosis), renal fibrosis, corneal fibrosis, fibrosis associated with skin and peritoneal surgery, fibrosis associated with burns, osteoarticular fibrosis or keloids.

8. A pharmaceutical composition characterized in htat it comprises a therapeutically effective amount of a peptide according to any of claims 1 to 3, with at least one pharmaceutically acceptable excipient.

9. A pharmaceutical composition according to claim 8, that comprises at least one peptide according to any of claims 1 to 3, with one or more TGF-β1 inhibiting compounds different from those object of this invention.

10. A DNA sequence that encodes a peptide according to any one of claims 1 to 3.

11. A DNA construct that comprises a DNA sequence according to claim 10.

12. A DNA construct according to claim 11 that comprises an operatively linked expression regulating sequence of said DNA sequence.

13. A vector comprising a DNA sequence according to claim 10, or a DNA construct according to either claim 11 or 12.

14. A host cell that comprises a DNA sequence according to claim 10, or a DNA construct according to either claim 11 or 12, or a vector according to claim 13.

15. Process of production of a peptide according to any of claims 1 to 3, characterized in that it comprises growing a host cell according to claim 14 under conditions that allow the production of said peptide, and it's recovery.

16. Use of a DNA sequence according to claim 10, or a DNA construct according to either claims 11 or 12, to inhibit TGF-β1's biological activity by gene therapy.

17. Use of a DNA sequence according to claim 10, or of a DNA construct according to either claims 11 or 12, in the manufacture of vectors and cells for the treatment of diseases and pathological alterations associated with excessive or deregulated expression of TGF-β1.